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13. ABSTRACT (Maximum 200 words)

Long-term potentiation (LTP) is widely regarded as a substrate for commonplace varieties of memory. The work supported by AFOSR grant 49620-92-0307 was intended to describe the cellular mechanisms responsible for the expression and stabilization of LTP. Three quite different lines of evidence (pharmacological, molecular, and biophysical) point to the conclusion that the potentiation effect is due to a change in the properties of post-synaptic transmitter receptors at glutamatergic synapses (AMPA receptors). Computer modelling studies indicate that a simple increase in the opening/closing rates of the receptors can explain LTP. Biochemical studies identified two LTP-related events that would promote the re-organization of the synaptic zone: *i)* activation of an intracellular protease (calpain) that cleaves essential proteins in the synaptic cytoskeleton and *ii)* a transient modification of adhesion molecules that results in the cleavage of their intracellular domains. Related work defined novel integrin-like adhesion receptors that appear to be needed for the stabilization of the potentiated state. AFOSR funded work also led to the synthesis of a new class of drugs (''Ampakines'') that ''up-regulate'' AMPA receptors; these compounds are the first to freely cross the blood-brain barrier and enhance excitatory transmission and LTP induction in behaving animals. ''Ampakines'' promote memory encoding in a variety of experimental paradigms without affecting performance variables. The drugs also reverse age-associated memory impairments in middle-aged rats; they are now being tested in young and elderly human subjects.

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Final Technical Report

AFOSR Grant # 49620-92-J-0307

"Synaptic Plasticity and Memory Formation"

Principal Investigator: Gary Lynch

6/1/92 - 5/31/95

A. Substrates of Long-Term Potentiation

A major portion of this AFOSR funded research program is directed at testing, extending, and elaborating the following hypothesis regarding the sequence of events that results in stable long-term potentiation (LTP):

(1) triggering involves NMDA receptors and increases in post-synaptic calcium;
(2) transient activation of calcium dependent lipases and kinases;
(3) modification of post-synaptic AMPA-type glutamate receptors and, in particular, their kinetic properties;
(4) activation of a calcium dependent protease (calpain) and destabilization of the synaptic organization via cleavage of adhesive and cytoskeletal proteins;
(5) reorganization and restabilization of synaptic anatomy via activation (or insertion) of integrin-type adhesion receptors;
(6) replacement of the cytoskeletal and adhesion proteins digested by proteolytic events occurring during LTP induction.

Step one (NMDA receptors and calcium) has become well established. Step two is generally accepted though controversies continue about which lipases and kinases are important. Beginning in 1988, a great deal of AFOSR funded work was directed at the locus of LTP; this ultimately led to the conclusion that potentiation involves post-synaptic modification of AMPA receptors and, in particular, a specific change in their channel kinetics (see below). The idea that LTP is expressed by a modification of AMPA receptors is now generally accepted. During the latter part of the tenure of the AFOSR grant, attention was shifted to steps four and five; i.e., chemistries that could destabilize and restabilize the synaptic junction.

1) AMPA-type glutamate receptors are the locus of LTP expression

Work carried out during prior AFOSR grants established by exclusion that LTP is due to a post-synaptic modification and not one involving spine resistance. The results pointing to a post-synaptic locus (no change in paired-pulse facilitation, no interactions with pharmacological agents that enhance release, little or no change in NMDA receptor dependent response components) have been confirmed by other groups. Major goals of the past AFOSR grant were to *i)* test the conclusion that modifications to AMPA receptors are responsible for expressing LTP and *ii)* if so, define the nature of the modifications. Three results pertinent to these points were obtained and are summarized in the following paragraphs.

- Changing the subunit composition of AMPA receptors blocked the capacity of hippocampal synapses to express stable LTP. Translational suppression of the GluR-A subunit of the receptor with antisense oligonucleotides was applied to cultured slices for 10 days. The resultant 30% loss of the targeted subunit was accompanied by a dramatic reduction in the incidence and magnitude of LTP. Thus, alterations in the make-up of the receptors profoundly and selectively affected their capacity to express potentiation (Vanderklish *et al.*, 1992).
- LTP is accompanied by changes in the waveform of the synaptic response. Alterations to the channel kinetics of the AMPA receptor would be expected to not only affect the size but also the shape of the post-synaptic response; this prediction was confirmed (Ambros-Ingerson *et al.*, 1992, 1993; Kolta *et al.*, 1995a).
- Induction of LTP changes the effects of AMPA receptor modulators on the size and waveform of synaptic responses (Xiao *et al.*, 1991; Kolta *et al.*, 1995b). This is as expected if LTP itself alters channel kinetics.

A five state model of the AMPA receptor was used in an effort to define the types of changes in receptor kinetics that could account for the LTP related effects noted above. This led to the surprising observation that simple increases in the opening/closing rates of the receptor channel would suffice to produce the various parametric and pharmacological aspects of LTP (Ambros-Ingerson and Lynch, 1993).

2) The binding properties of AMPA receptors are markedly influenced by a factor or factors found in the synaptic zone

The mounting evidence that LTP is due to a specific change in AMPA receptor properties led to a gradual switch in the laboratory's emphasis from physiological analyses of the potentiation effect to a biochemical search for the synaptic factors responsible for the receptor modification. Several studies of this kind were completed during the tenure of the grant First, it was established that solubilization of AMPA receptors from synaptic membrane fractions profoundly increases their affinity for agonists but not antagonists (Hall *et al.*, 1993a) and that this effect is *not* due to a shift of the receptor into a desensitized state (Hall *et al.*, 1993b). It thus appears that some element in the synaptic environment maintains the AMPA receptor in a particular state; it should be noted that this extreme dependency on the synaptic region is not reported for other ionotropic receptors (e.g., the NMDA subclass of glutamate receptors co-localized with AMPA receptor; GABA receptors). Second, it was shown that treatments which disrupt protein-protein interactions (UV radiation, thiol reducing agents) convert membrane bound AMPA receptors into the high affinity state characteristic of solubilized receptors (Hall *et al.*, 1994a). This result strongly suggests that a protein present in high concentrations in the synaptic zone regulates the properties of the AMPA receptor. Third, heparin converts soluble receptors into the low affinity state characteristic of receptors bound to synaptic membranes (Hall *et al.*, in prep). Heparin is known to cause protein aggregation and evidence was obtained from size exclusion columns and ultracentrifugation that it has this effect on AMPA receptors. Immunoprecipitation experiments showed that no proteins were tightly associated with AMPA receptors after heparin treatment. Accordingly, we now advance the hypothesis that clustering (aggregation) of AMPA receptors changes their functional properties and that this is the mechanism whereby the synaptic environment controls receptor operation.

Previous work from this laboratory had indicated that cytoskeletal/structural changes occur in the synaptic region in association with LTP. It can be assumed that such modifications affect the distribution of transmembrane proteins such as the AMPA receptor; if so, then the structural changes would also alter the probability (frequency) of receptor-receptor interactions and hence alter the properties of the receptors.

3) Calpain is activated during LTP induction and plays an essential role in the production of stable potentiation.

Work carried out in this laboratory showed that spectrin, a primary constituent of the post-synaptic cytoskeleton, is an excellent substrate for calpain and that its cleavage by the protease results in a stable breakdown product (BDP). Other groups have developed antibodies specific for the BDP and we have confirmed their findings. These results have provided the bases for an immunocytochemical assay for *in situ* calpain activation. Studies conducted during the tenure of the AFOSR grant using this assay have shown that the patterns of synaptic activity typically employed to induce LTP stimulate calpain in what appear to be spines and dendrites. Specifically, theta burst stimulation caused the formation of the spectrin BDP in fine dendritic branches and spine-like puncta in the zones containing activated synapses (Vanderklish *et al.*, 1995). Besides providing the first demonstration that repetitive synaptic activity can trigger calcium dependent proteolysis, this result satisfies a necessary prediction of the hypothesis that calpain plays an essential role in LTP formation (i.e., that inducing stimulation is sufficient to activate the protease).

4) Translational suppression of calpain blocks the formation of stable LTP.

Past studies from this laboratory, and confirmed elsewhere, demonstrated that drugs which block calpain activity suppress the formation of stable LTP. The lack of specificity of available inhibitors weakened the strength of the conclusions drawn from these results (see past Progress Reports). This led us to use transfection with antisense oligonucleotides in an effort to reduce the levels of calpain in cultured hippocampal slices. A procedure

was ultimately developed that resulted in a 50% reduction of calpain protein and activity; the slices also exhibited a substantial reduction in NMDA induced proteolysis of spectrin (Bednarski *et al.*, 1995). Subsequent experiments then showed that slices with reduced levels of calpain fail to exhibit stable LTP; controls included slices treated with sense oligonucleotides (Vanderklish *et al.*, in prep.). These results, together with the above mentioned pharmacological findings, constitute strong evidence that calpain is essential to the formation of stable LTP.

5) The triggering event for LTP causes the extracellular proteolysis of neural cell adhesion molecules (NCAMs).

Calpain, by cleaving spectrin and other post-synaptic structural proteins, can be assumed to disorganize the synaptic cytoskeleton. The cytoskeleton together with transmembrane adhesion receptors provides the substratum around which the anatomy of the synaptic zone is arranged. It was thus of interest to ask how the adhesion molecules are affected by induction of LTP and how they might contribute to the stabilization of the potentiated state. AFOSR funded work conducted during the past year resulted in the unexpected observation that brief stimulation of NMDA receptors causes the *extracellular* proteolysis of NCAM; this effect is rapid (< 1 min) and results in the transient appearance of a soluble 75 kDa fragment. Subsequent studies have identified protease inhibitors that block the effect (Hoffman *et al.*, in prep.); experiments are now in progress to test the prediction that the drugs will block LTP. If the prediction is confirmed, then a major effort will be undertaken to isolate and characterize the synaptic protease responsible for cutting the extracellular domain of NCAM. In any event, the results collected so far describe a second, LTP-related event (calpain activation being the first) that should reduce adhesion and hence destabilize the synaptic junction.

6) Evidence that integrin-like adhesion receptors participate in the stabilization of the potentiated state.

Prior AFOSR funded research led to the conclusion that an integrin-like receptor contributes to the stabilization of LTP and identified candidate proteins for this receptor. More recently, studies were conducted using a novel peptide that has recently been shown to block integrin receptors of the "RGD" type; i.e., the subclass to which the previously identified candidate for a synaptic integrin belongs. Infusion of this peptide into slices blocked the stabilization of LTP with no evident effects on baseline physiology or the transient short-term potentiation (STP) that accompanies LTP. Further work showed that integrin antagonists prevent the stabilization of LTP even when infused 5-10 minutes *after* induction, thereby confirming the idea that activation of the adhesion receptors is a very late event in the stabilization process (Bahr *et al.*, 1995). Efforts are now under way to identify the gene which encodes the candidate for the pertinent integrin.

B. A Novel Family of Centrally Active Drugs That "Up-Modulate" AMPA-type Glutamate Receptors and Enhance LTP

As described in last year's Progress Report, AFOSR funds were used to design, synthesize, and test a new class of drugs ("Ampakines") that act on the kinetics of the AMPA receptor channel so as to enhance the ion currents it passes. It was known from earlier work in the laboratory that drugs that produce such effects substantially reduce the amount of afferent activity needed to induce robust LTP in brain slices; given the evidence linking LTP to memory, it was reasonable to assume that drugs producing such effects in behaving animals would potently facilitate the encoding of memory.

1) "Ampakines" modulate AMPA-type glutamate receptors, enhance glutamatergic transmission, cross the blood-brain barrier, and promote LTP

Excised patch studies have shown that Ampakines prolong the duration of AMPA receptor-mediated currents in a fashion that has a very rapid onset and washout (Arai *et al.*, 1994). Comparable effects are observed on synaptic responses recorded from *in vitro* brain slices (Staubli *et al.*, 1994a). PET scan experiments using ^{11}C-labelled drug indicated that the drugs reach the rat brain within *one minute* of the intraperitoneal injection and equilibrate at high concentrations within 2-5 minutes; physiological recording from freely moving rats confirmed that the drugs have a very rapid onset of action after peripheral administration and remain effective for 90-120 minutes. These latter studies also revealed that Ampakines produce the expected facilitation and prolongation of synaptic responses *in situ*; these drugs are thus the first compounds known to enhance fast, excitatory transmission in brain. Finally, chronic recording experiments have demonstrated that the AMPA drugs markedly reduce the number of afferent stimulation bursts needed to induce LTP in behaving animals (Staubli *et al.*, 1994b).

2) Two subgroups of drugs are present in the Ampakine family.

More than thirty functionally effective analogues have been synthesized with the latest variants having a potency more than 100 times greater than the original drug. Studies using excised patches revealed that the compounds fall into two groups, those with greatest effects on steady state current vs. those with equal effects on steady state current and rate of desensitization. The latter compounds affect binding of agonists to the AMPA receptor while the former do not. A model of the AMPA receptor has been developed and used to make explicit predictions about the channel kinetic parameters affected by the Ampakines (Arai *et al.*, 1995b; also Kessler *et al.*, 1995).

3) Ampakines have differential effects on the subunits of the AMPA receptor.

AMPA receptors are thought to be pentamers composed of subunit proteins referred to as GluR-A - GluR-D, with the GluR-A,B,C units being prevalent in the forebrain. Each of the subunits has two splice variants ("flip" and "flop"). The balance of subunits varies across brain regions and cell types, a point that is of considerable significance given that the different subunits have different pharmacological and biophysical properties. It is thus possible that the effects of AMPA receptor modulators will vary across AMPA receptor subclasses (i.e., classes with different fractional concentrations of GluR-A,B,C) and hence brain areas. Several approaches to this issue are being developed, one of which is the preparation of clonal cell lines that express homo-oligomeric AMPA receptors. This has involved a collaboration with laboratories at Harvard (R. Neve) and the University of Heidelberg (P. Seeburg). So far, stably transfected lines with pure GluR-A, GluR-B (flip), and GluR-C have been prepared; GluR-B (flop) is also close to being ready. Hetero-oligomeric cells have also been prepared (GluRA-C) but it is not yet clear if these are clonal.

Two major results have been obtained. First, GluR-B appears to be the subunit that is essential for the low affinity state of the two state AMPA receptor. Second, Ampakines have a considerably greater effect on GluR-C subunits than on GluR-A (Hennegriff *et al.*, 1995). Other work carried out during the past year in collaboration with C. Gall indicates that the relative balance of GluR-A vs. GluR-C varies substantially across forebrain (Gold *et al.*, 1995). The possibility that Ampakines act in a regionally differentiated fashion is thus very real. Tests of this are planned for the coming year.

4) Ampakines have greater effects and a lower apparent threshold of action on complex networks than on monosynaptic transmission.

Two studies showed that, as predicted, the effects of the AMPA receptor modulators become amplified across serial synaptic connections (Arai *et al.*, 1995c; Sirvio *et al.*, 1995). The result is important because *i)* it indicates that Ampakines will have a much greater influence in the enormously complex circuitries associated with higher order, cortically mediated behaviors than on simpler, reflex-like functions and *ii)* behaviorally effective dosages will be somewhat lower than might be predicted from studies of monosynaptic transmission.

5) "Ampakines" enhance memory

The drugs have been shown in studies from five laboratories to improve memory across a variety of behavioral tasks including the following:

i) recent memory in radial mazes (Granger *et al.*, 1993; Staubli *et al.*, 1994a,b),
ii) olfactory match to sample (Staubli *et al.*, 1994b),
iii) eyeblink conditioning to a tone (Shors *et al.*, 1994),
iv) two odor discriminations (Staubli *et al.*, 1994a; Larson *et al.*, 1995),
v) conditioned fear responses (LeDoux *et al.*, 1994).

In certain of the above experiments, it was possible to measure the effects of the drugs on performance during acquisition (Granger *et al.*, 1993; 1995; Larson *et al.*, 1995; Shors *et al.*, 1994). These analyses have shown that the AMPA drugs at dosages which do not increase arousal, alter response latencies, or affect balance beam performance are effective in improving retention.

6) Ampakines facilitate the firing of cells encoding spatial locations and reverse age-associated memory impairments for spatial cues.

In the past year, the drugs were shown to enhance the firing of "spatial cells" in freely moving rats and to offset the marked decline in spatial memory that occurs in middle aged animals (Granger *et al.*, 1995).

7) Ampakine effects in human subjects.

The Ampakine BDP-12 was found to have minimal side-effects in human safety trials (Lynch *et al.*, 1995) and results from memory tests are now being analyzed. A large scale formal study of the drug's actions on memory encoding is in progress.

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